

(19)日本国特許庁 (J P)

(12) 公表特許公報 (A)

(11)特許出願公表番号

特表平8-511696

(43)公表日 平成8年(1996)12月10日

(51)Int.Cl.⁶
A 61 L 27/00
33/00

識別記号
7019-4C
7019-4C

府内整理番号

F I
A 61 L 27/00
33/00

M
T

審査請求 未請求 予備審査請求 有 (全42頁)

(21)出願番号 特願平6-524763
(86) (22)出願日 平成6年(1994)5月9日
(35)翻訳文提出日 平成7年(1995)11月10日
(86)国際出願番号 PCT/CA94/00257
(87)国際公開番号 WO94/26321
(87)国際公開日 平成6年(1994)11月24日
(31)優先権主張番号 08/058,753
(32)優先日 1993年5月10日
(33)優先権主張国 米国(US)
(31)優先権主張番号 08/226,345
(32)優先日 1994年4月12日
(33)優先権主張国 米国(US)

(71)出願人 ユニヴェルスティ・ドゥ・モントリオール
カナダ国ケベック アーシュ3テ 1ジ
4, モントリオール, エドワール-モンブ
ティ 2900
(72)発明者 ナンスイ, アントニオ
カナダ国ケベック アーシュ9ペ 3ジ
3, ドラール・デ・オルムオー, セレス・
ストリート 9707
(72)発明者 マッキー, マルク・デ
カナダ国ケベック アーシュ9エール 5
エス1, ポワント・クレール, ドネガ
ニ・ストリート 585
(74)代理人 弁理士 湯浅 茂三 (外6名)

最終頁に続く

(54)【発明の名称】 結合改良のためのバイオアクティブ共役体による移植片表面の改質

(57)【要約】

本発明は、金属移植片外面を被覆するために適したバイ
オアクティブ共役体であつて、下記構造式I：

-R-X-P-

【式中、Rは移植片表面に共有結合するに適したO又
はSであり；Xは結合、少なくともC、N、O、S1若
しくはSの1～30個の共有結合原子の直鎖若しくは分
枝鎖、少なくともC、N、O、S1若しくはSの1～2
0個の共有結合原子の環、及びこれらの組合せから選択
され；Pは組織成長、安定化及び統合を促進する共有結
合したバイオアクティブ分子部分であり、前記部分はそ
の生物学的活性を保有する】で示される前記バイオアク
ティブ共役体に関する。本発明はまた、バイオアクティ
ブ共役体による移植片の共有結合被覆方法をも関する。



二二二 1

○

○

(4)

‘ ¥ % W | ■
P P D O L ~ — » “ — — o b t @ ■
X L ■

P Q D 1 ☒ ' fi A — ¥ ° ■
° f — | u ^ m [| ^ m [■
» w I / ' ~ E — f ■
P R D O L | e V I X ^ e B b N d ■
‡ ☉ A A — “ ' ^ ' » ¢ ■
P S D E — f fi A — ¥ ° § ~ ■
β ■

Y >

Z

%

O C I ■

A — ¥ ɔ

> ■

i j > " "

{ > " " g D » « ■

o C I A N e B u ■

i j s Z p

v [g A B A s A , ɿ ɿ ~ f o

A " ¥ ɔ " i v I [• Ø % ■

~ A " j % " " - L ■

~ q g i ¥ ɔ A ‡ ɺ Ø B ■

ɔ ɺ " A A ‡ ɺ % " " G • ■

Ø B - K v " A - ɺ - " A E ■

" u i o ^ / W j i R ■

j / " > x ɔ ɛ ' ¥ < ‡ ɺ ɔ ɺ ‡

ɺ Ø ' R ¥ ɔ ~ > ɔ ' < - « " ɸ ■

« . - ' % B , s " ɿ ɿ % ɺ ~ ɺ g

. ^ " l H " ~ ' R " ~ ■

" ~ ɔ L A A — ¥ ~ » ɺ

£ " . ■

. B @ - A - ~ m ɺ Ø O " ■

~ L p / " A X " O " p r A E ■

p r " (body fluid) ' ~ ɛ I ■

` fi - » ‡ ɺ " ɔ fi " ' ¥ ‡ A

- ɺ S Z P A - " ■

T ^ I A j % L - " A ■

p ɔ ɺ ɺ ~ ɔ Ø B - ɺ v [g " ~ ■

[g " » / ɛ Y g D ɺ Ø ■

C Y " T O ° - Ø ~ w f ‡ E ~ ¢ Ø " 
 ¢ B E T C Y " T O ° L < ¢ E 
 E Ø - ~ 

O " p A - Z g p ¢ ~ 
 - < • e • Ø - A - 
 , A - - L . • Ø - m 
 [‡ % E ð ¥ ° " ^ f Anchoring surface) @
 B I > x " s " i - < > e ð ‡ E 
 L ~ ~ ‡ E  (weakening) R 
 " ¢ ð o ¢ p ¶ ¶ Ø ' - 
 - - ~ " A - - S - - > 
 @ B I ' • Ø % 
 % A - ¥ < ‡ E ~ ¢ Ø B ' A - 
 E ~ ¢ Ø ~ ¢ / S > ° ~ A 
 E ~ ¢ " ¢ B - a , s " A ¥ ° 
 ¶ ~ ¢ % B m / A - L ° g 
 oreign body) ~ ~ p • Ø A - ~ 
 - ~ " - < Ø L 
 g ... O - ~ ' R C U 
 j " A A ‡ E Ø ¥ ¢ ~ ð I fi 
 ¢ > x < ¢ v 
 o ... O - ~ ' 
 Q S æ j " A - fi ¢ ð ~ » 
 " I L Ø % E ð ~ ' < Ø 
 f • Ø B ¥ ° a % E ð ~ " A 
 < - < Ø f o C X • Ø % d 
 e ... O - ~ ' S C Q 
 j " A % d a o s Z p A - ¢ 

A	V	e	B	~	~	A	~	D	»	œ	œ	co-lo						
calization)	...	A	·	~	~	C	~	O		A								
•	Ø	~		f		~		i	q	f	c	j						
Œ	~	¢	Ø	i	s	o						W						
<hr/>																		
¶	A	-	Œ		^	p	N	ɛ	"	z	y	‡						
p	N	ɛ	"	‡	@	¤	»	g	D	~	‰	¥						
J	n	A	†		A	æ		g		g	b	N	X					
"	w	.																
D	q	D	C	Q	R	S	F	S	V	X	~	S	X	Q	i	i	D	a
<hr/>																		
1																		
B																		

» i

[φ B fl l A N ' | bi D c bi
D C V Q

> _____ ∇

> " f - | u ^ m [| ^ m [
 » u ' <
 ‡ > " A { > Ø B @
 f - | u ^ m [| ^ m [
 ostatic) d C » w I - Ł A - E " ^
 ~ { • Ø -
 A - ¥ ° E - f " fi . q

 - ¥ ° § %
 ‡ > " A { > Ø B @
 - z m g n ^ m g n / " A - o
 x φ ~
 } ° " p
 } P " A b g a Ł f x fl Ø »
 ^ - E
 } Q " A ^ p N Ł I X e I |
 eled) L @ x Ł ~ ^ f • A a Ł x fl
 ° ^ - Ł G
 } R " A I N ^ f V ' I [w L
 w l d q " l @ ' ~ E % Y f
 % I N ^ f V '
 } S " A I N ^ f V ' I [g " t
 l @ ' ~ E %
 } T " A I N ^ f V ' I [g " t
 l @ ' ~ E %
 } U " A I N ^ f V ' I [g " t
 l @ ' ~ E %
 } V " A { > ' ~ > φ ‡ E %
 ¶ x w I « oe

} W " A P S C L x [V ¥ % W |
 / ¶ x w I « ¶
 } X " " (chicken) - Y (raised) A ' ' , §
 N [i R I X e I | ' R ¶
 } X a " A } X ' p ¢ % ' fl ¶ ¶
 g a £ < • v [g x fl Ø . D » ¶
 ' u E ¶
 } P O ' " A E T M R } E X A Q ¶

 G i i } g b N X x fl Ø fi S ^ ¶
 g G
 } P O a " A ¥ ' ' b g P t ¶
 £ ^ p N (immunodetection)
 } P P " A fl ¥ » Z % A J ' I [¶
 ' ¶ f • w o ¶
 } P Q " A A J ' ^ ¥ ' ¶
 g £ » ' f • ¶
 } P R " A A J « z X t @ ^ [[¶
 t u X y N g ¶
 } P S ' " A E ' I o ' £ ' ¶
 - q A j ¶ f • A £ p ' ¶
 E f
 } P S a " A I o ' £ ' i o j z ¶
 w i - q A j ¶
 } P T " A a t - f ‡ E Ø A { > ¶
 X L [¶
 > _____ "
 { > o C I A N e B u / " A ¶
 A - E . x fl Ø g D < • A £ » y ¶

¥ ₩ ₩ ₩ | ₩

o o t æ A A -

‡ A { > o C I A N e B u /
z ß • Ø \$ ð A g D | A - E .
\$ ' A A - a ' < - █
- o C I A N e B u / " g D █
fl Ø A - ' D " █
} P " » E - æ ç █
} Q - " A d q , ~
~ @ • Ø - " - < A - C " g █

¶	<	^	p	N	ξ	~	m	F	‡	€	£
%		D	¢	^	p	N	ξ	■			
}	X	‘	”	A	—	”	”	—	Y	¶	‡
I		‘		R			Ø	C	m	u	b
	‘	R	”	b	g		’		»	‡	€
[P	A	b	g	•	A	u	~	G	[]
[R	A	,	»	b	g	I	X	e	I	‘
‘	A	l	D	b	D	e				b	
e	L	T	X	w	A	q	[■			
}	X	a	”	A	R	I	X	e	I		‘
		‘	u	E	»	w	W	fl		■	
X		}	g	b	N	X	i	.	D	»	■
€	%	A	—	^	p	N	■	‘			
D	C	Q	R	F	S	V	X	‘	S	X	Q
	D	CW	F	S	W	T	‘	S	X	U	■
—	E	°	”	A	.	(scaffolding)	h	^	L	E	
t	•	Ø	‡		”	•	<	•	¶	¶	%
X					f	(remodeling)			A		E

C	h	j	ø	ɸ	~	-	fl	ɿ	^	p	N	ɛ
"	^	g		h			‰	~	«	fl	l	█
X	e	I		'		L	L	@	w	"	█	
}	P	O	"	A	"	β	o		(reduced)	G	i	
"	^	Z			~	A	@	¥	I	a	'	•
	^	k			C	l				c		
<hr/>												
C	m	D	x	D	C	Q	"	C	D	v		█
G	i			ɛ	¥	°	'		"	£	•	∅
f		A			A		œ	a	t	█		

C g		C	X	X	F	R	Q	P	'	R	R	P	g
	< n æ G i	L	E	"	A	G	i			z			
	a (post-secretory cell)	-	L	A				A	»	E	G		
•	Ø	E w	"	A	-	E		^	P	N	z		L
Ø	E L		"	i	a		^	G		Z		g	"
~		« »											
-	~	"											
	A	^	b	'									
"	G i		z	^	p	N	z	¥	»	•	Ø	-	"
B	G i		z	^	p	N	z	"	{	z	I	Q	
Q	j	i	G	i			j	'	<	L	A	-	E
fl	Ø i m		L	b									
	a		r		C	P	R	"	F	R	P	R	g
	j	ø	ç	~	T	L	d	D					

" -
 æ A » % E - f ~
 A N e B u / Ø - L
 ' Ø ¥
 i j fi S " » i
 15 q ^ - L A t i s j ¥ ° x
 ... a - Ø -
 q " æ P T •
 - Ø - A
 16
 q ¥
 I
 Q
 15 P D
 16

 S F r F b S P D U
 i j l f
 ' ^ i s j " % « fi - Ø - A
 A - E " e
 r Ø s ¥
 ,
 表 1

官能化アルカンチオールによる処理後の還元チタン表面における原子%

処理	O	Ti	C	S
SH-(CH ₂) ₂ COOH	35.7	7.3	53.9	2.1
SH-(CH ₂) ₂ COOH/H ₂ O	43.2	15.4	7.2	2

a L ¥ P (aqueous exposure) Ø ~ a » w I
 r

} P P " ' ^ ' I [■
 } P Q (aqueous treatment) a ' i ' I [■
 » " " ç - ■
 { > " " ■ • Ø - " " > { ■
 A Q ^ • Ø - ^ ' ~ A { > " ■
 _____ { ■
 I N ^ f V ' I [g ■
 T v †
 ' ^ fi A ~ i o D P . ■
 g - P T " . " g » w N [j ■
 P F P Q F V e . f - | u ^ m ■
 ç ~ R O " d C » w I / • Ø B - ■
 † © Ø d C » w I m § • Ø B ■
 ~ ç " ç " A p ç % B @ " ' ■ (measureable) »

Ø B
 - © " A I N ^ f ■ | i b j, | r g ⁻³ POL ' D
 - l w L T n m t b V f { b N X ■
 ~ A % < . " ' ^ ¥ . ~ ■
 " > A - fl ' I [n t © ■
 † " A ■
 | - S - (CH₂)₁₇ - CH₃
 Ti 表面 |
 | - S - (CH₂)₁₇ - CH₃

/ " ' R W < P W ' < A - P ■
 " O T V W L T ■
 " " ■
 P ç Ø ¥ . " " B @ " W 1 d q " 1 ■

" 1 @ i d r b ' j ~ ~ . E Ø B - B

o . (emitting atom) d q S x < † c • "

ç V t g ¥ † E Ø ~ ç / - L • Ø

' ¥ ~ A † (close-lying) s [N " ¥

• Ø ¥ t g E F A

' ^ œ o G l M [x ç ~ ,

w ' ~ ç † E % fi S % " ' ^

æ R O - Ø B S T - < L a

ç " A fi S " ' I [g

° ^ Ø

Y t } R ' U " A X y N g T ^

N g - L A } S " - f X y N g -

U " ' ^ X y N g - Ø B Y f -

d q ' > I • Ø - L A e s [N

s [N l f E Ø

... B - " A ' ' ^ ' s [N "

Ø - L A s [N y A " " Ø '

A - E s [N l f

' ^ " m o ' ¥ - Ø ~ ç /

- ' ; • Ø B Y f - f ^ > R

[j o ' I [t (point-to-point variability) "

Ø - ' f • B ' A ' ^ ...

Q D T ... Z -

{ Ø

' ^ A - A J

» % ' ^ A - A { E h q

w L T f J ' I [- " A Q T %

o " A O D P l - o b t @ [O

% B A - o b t @ [- • • < **█**
 J < z X t @ ^ [[i E V S ' **█**
 A Q T ☐ ☐ ~ P Q h a % B - **█**
 ☐ % B k █ i D a █ D C P █ S F R Q P
 X S U j j ' ~ **█**
 { E h _____
 ' ^ A - A J **█**
 » % ' ^ A - A { E h E **█**
 » fl # " % B **█** " ☐ ☐ ~ Q A **█**
 | A ~ m v s g G g L V V **█**
 % (modified) A - A { E h h q % O **█**
 J < z X t @ ^ [[/ L █ i D a
█ D b █ D C P █ S F R Q P i P X S U j j **█**
 } W " A A - ☐ ° / L % A **█**
 L x [V a » ☐ ☐ w I < **█**
 S O T ☐ fl Ø s [N o » f • **█**
 > - " L # E % } V " { z I ☐ I **█**
 x " y f G } ' " Ø | j g **█**
 _____ { E
 S z A J < z X **█**

} P T " A a A ^ b ' g x c ■
 ¥ . A - X ■
 { > » ' L { l ~ ■
 L A - o L " E . { > . ■
 • Ø / } † E A { > J f ' ■
 " m " K I " { ~ ~ ■
 ~ A y " L ē " "] / ■
 B

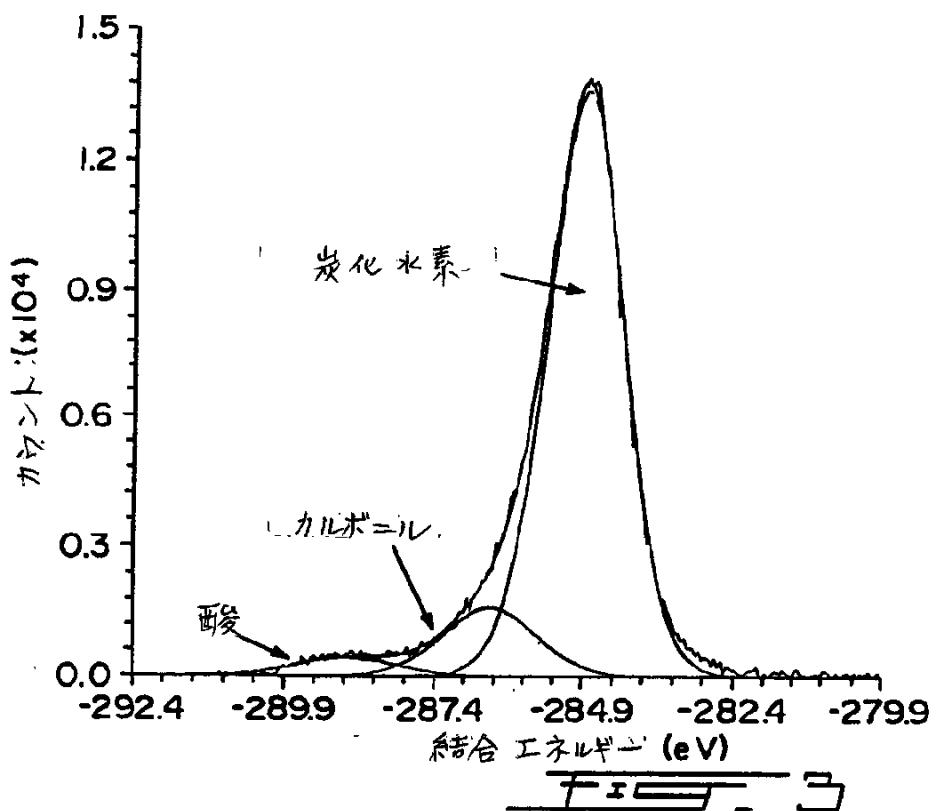
Y } ■

正反1

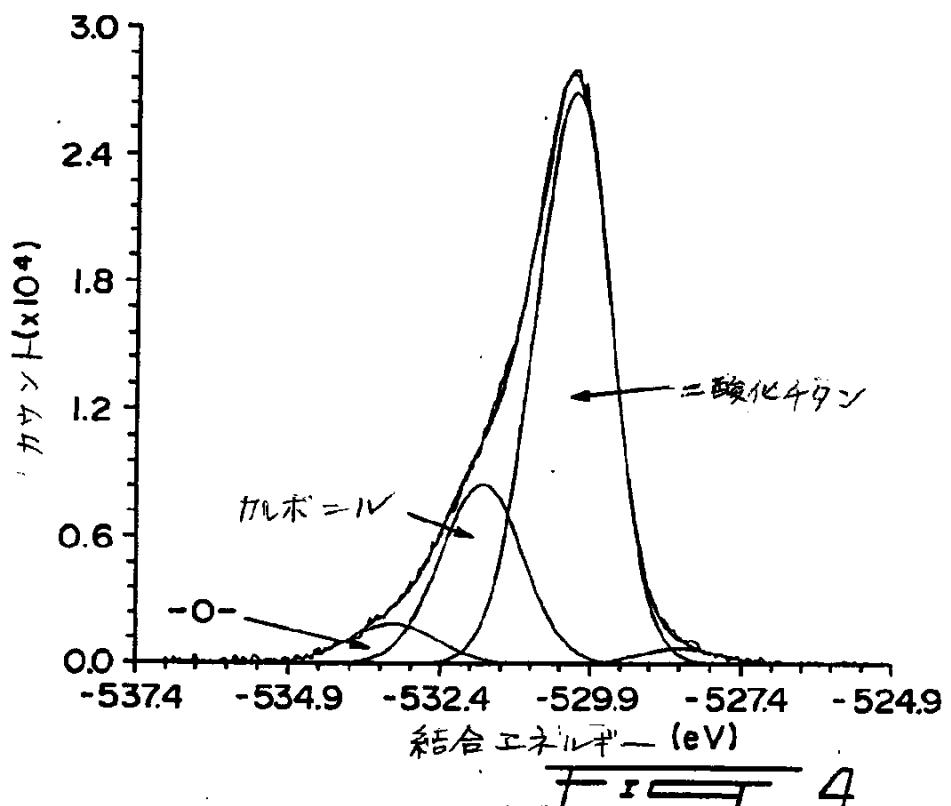
Y } ②



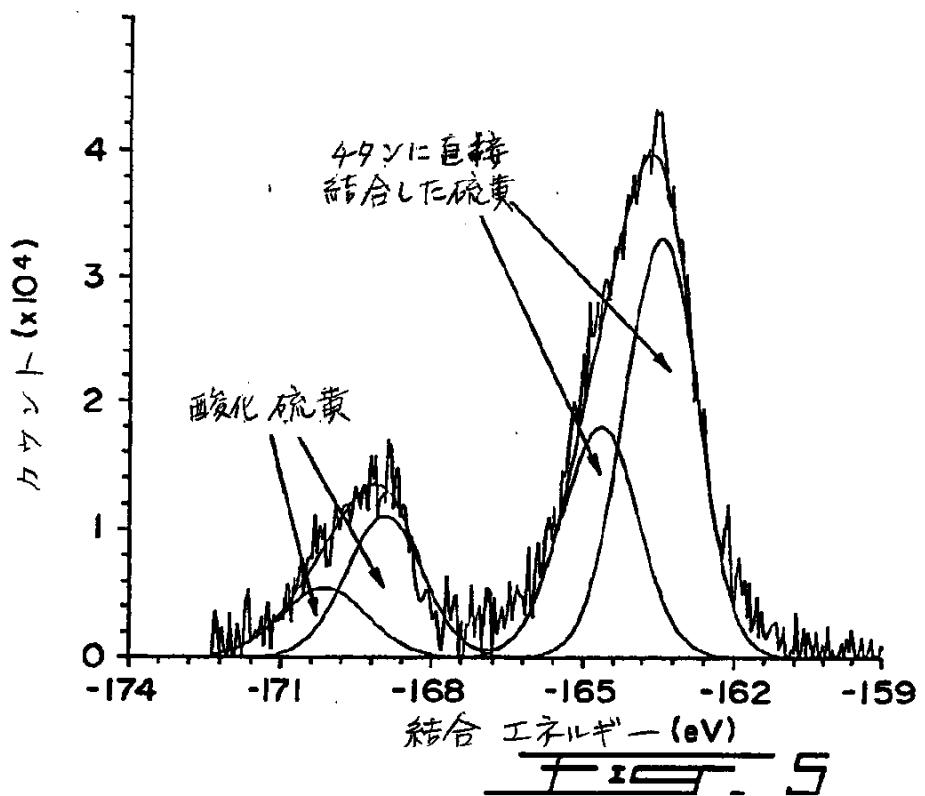
Y %



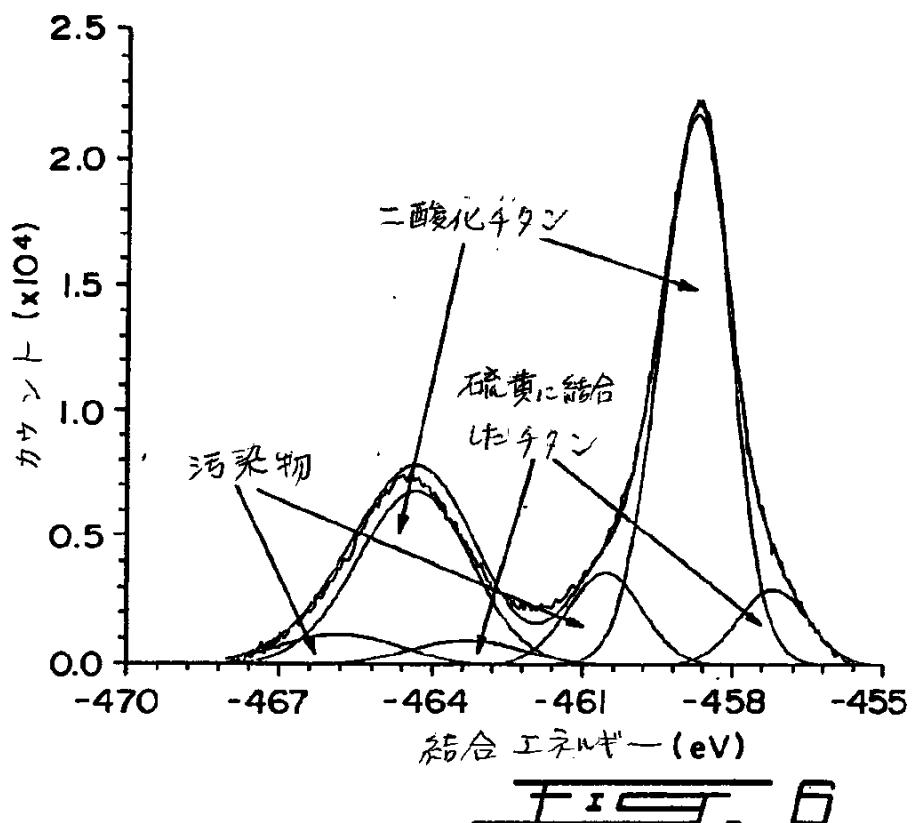
Y } S



Y } Z

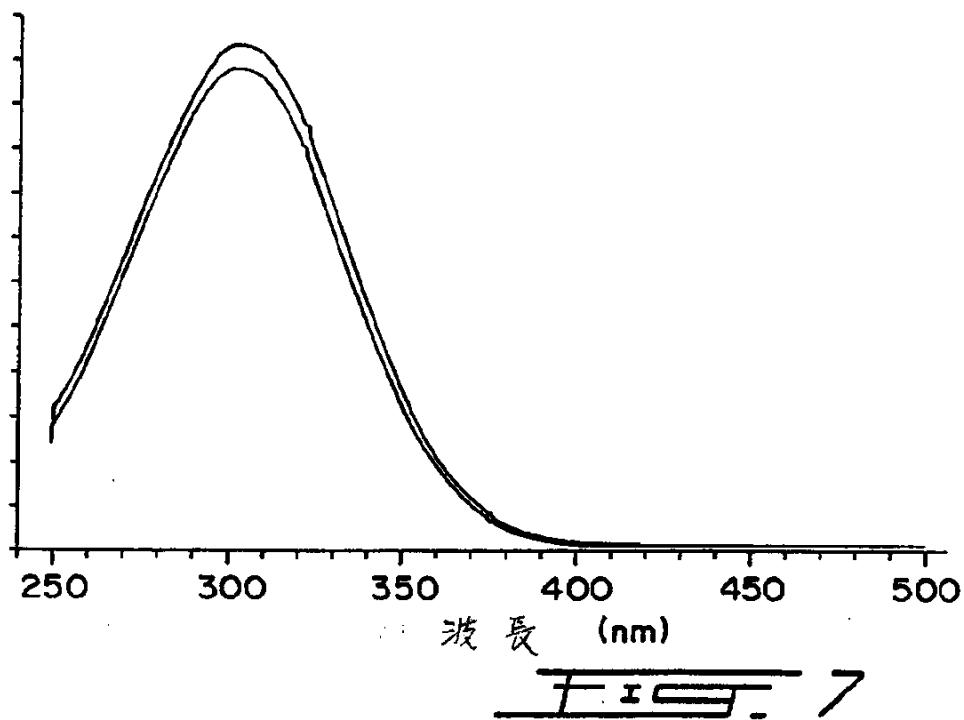


Y %



Y } ■

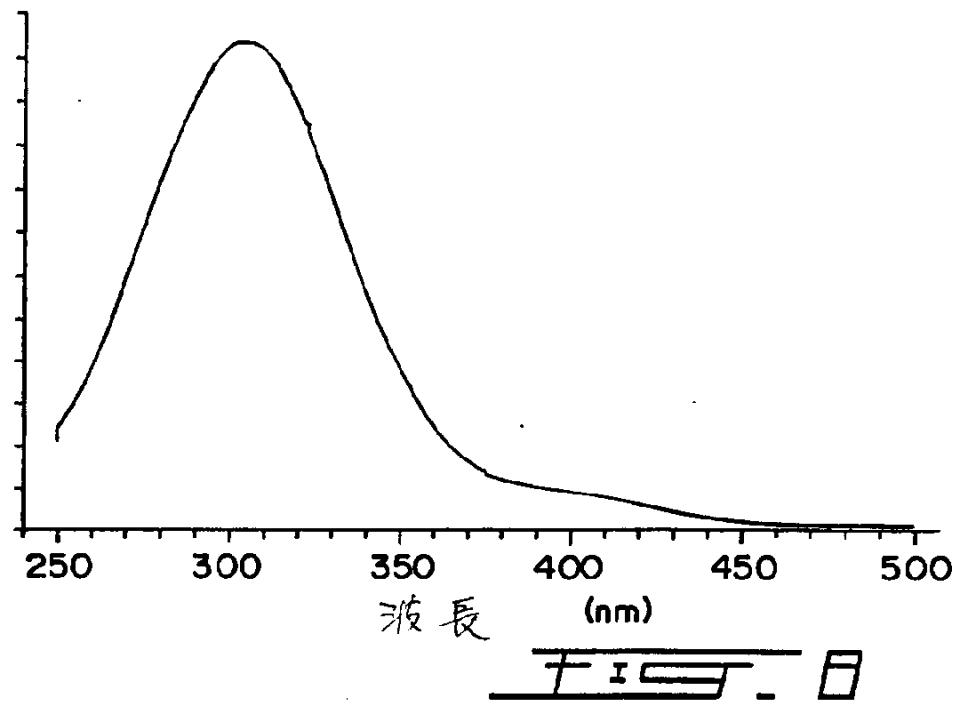
吸光度



—
—
—
—
—

Y } ■

吸光度



—
—
—
—
—

Y } X

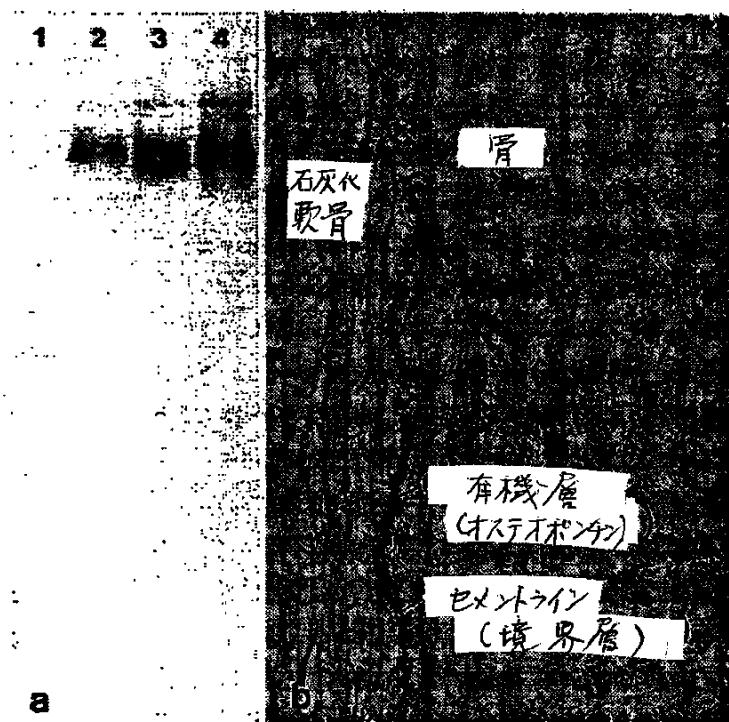


FIG. 9A FIG. 9B

Y } ②

1 2 3 4 5 6

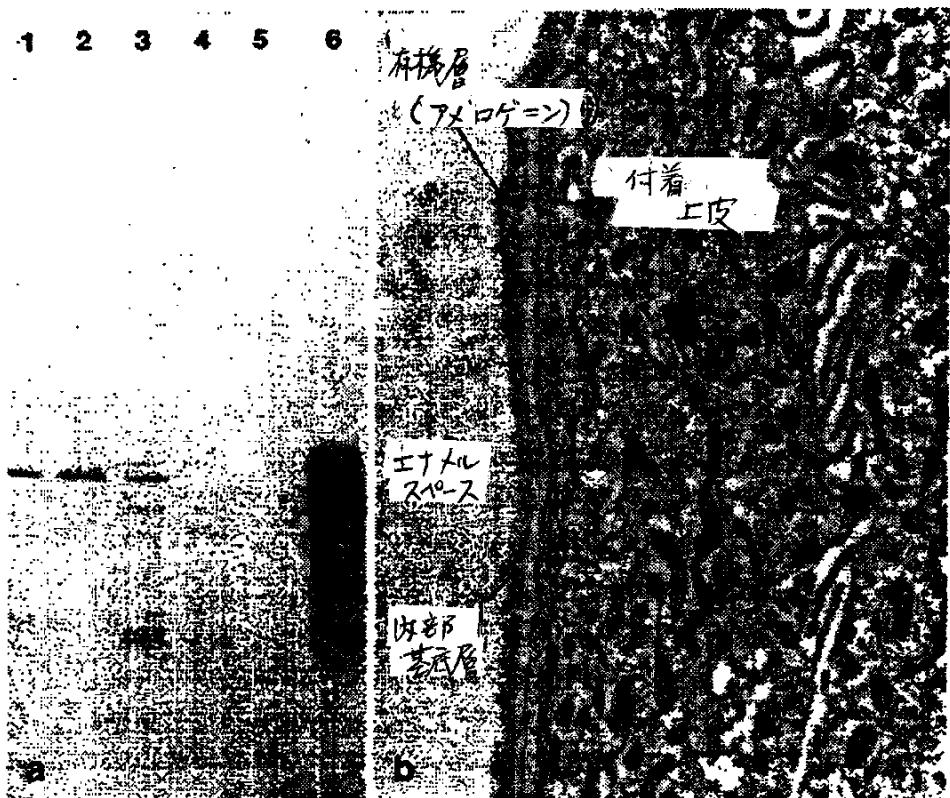
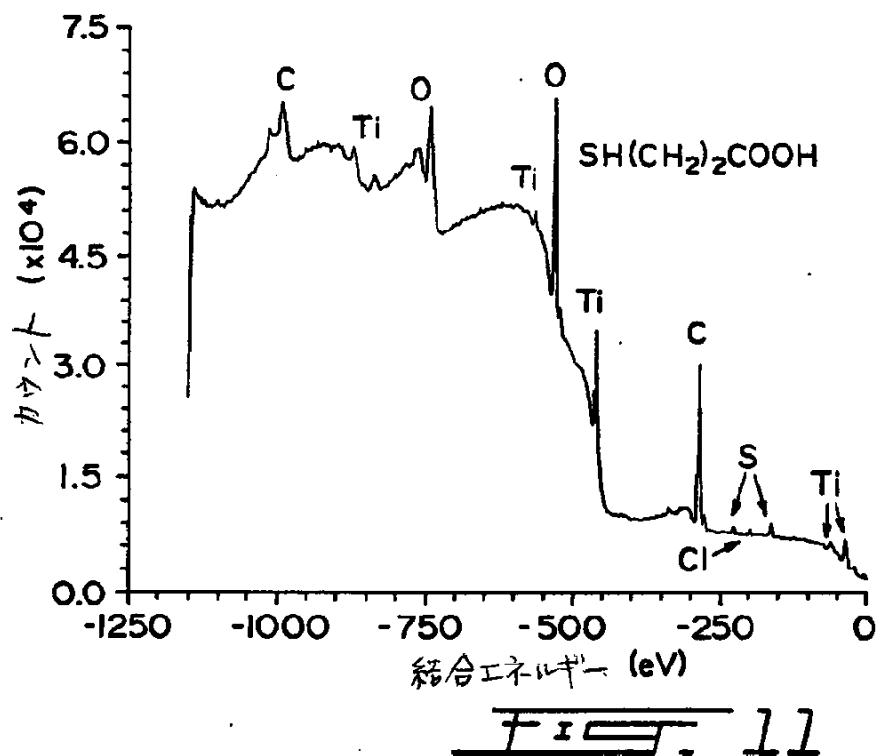
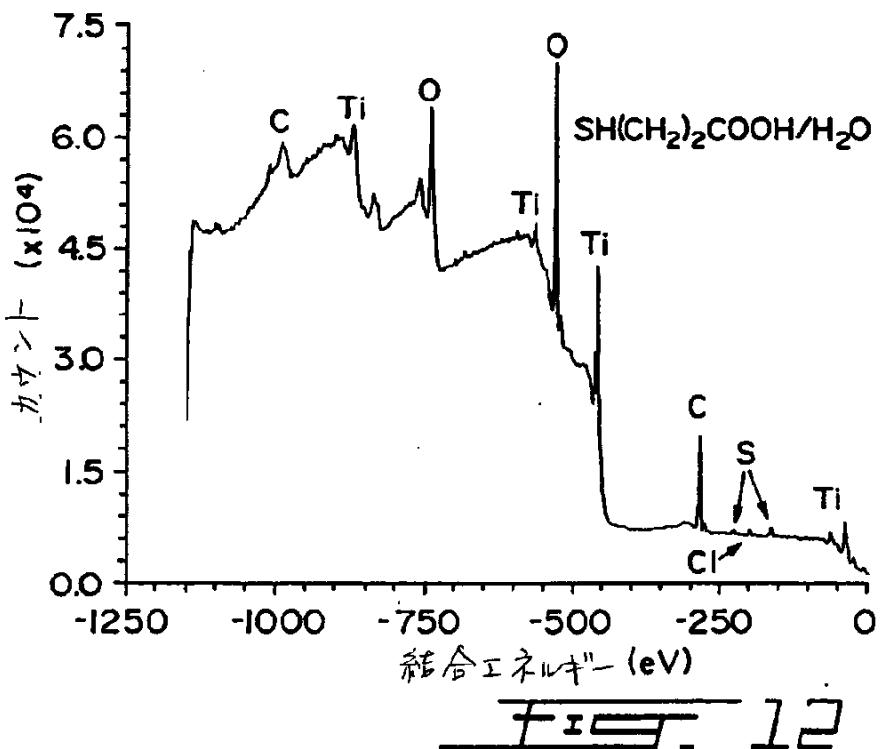


FIG. 10A FIG. 10B

Y } E



Y %



Y % R

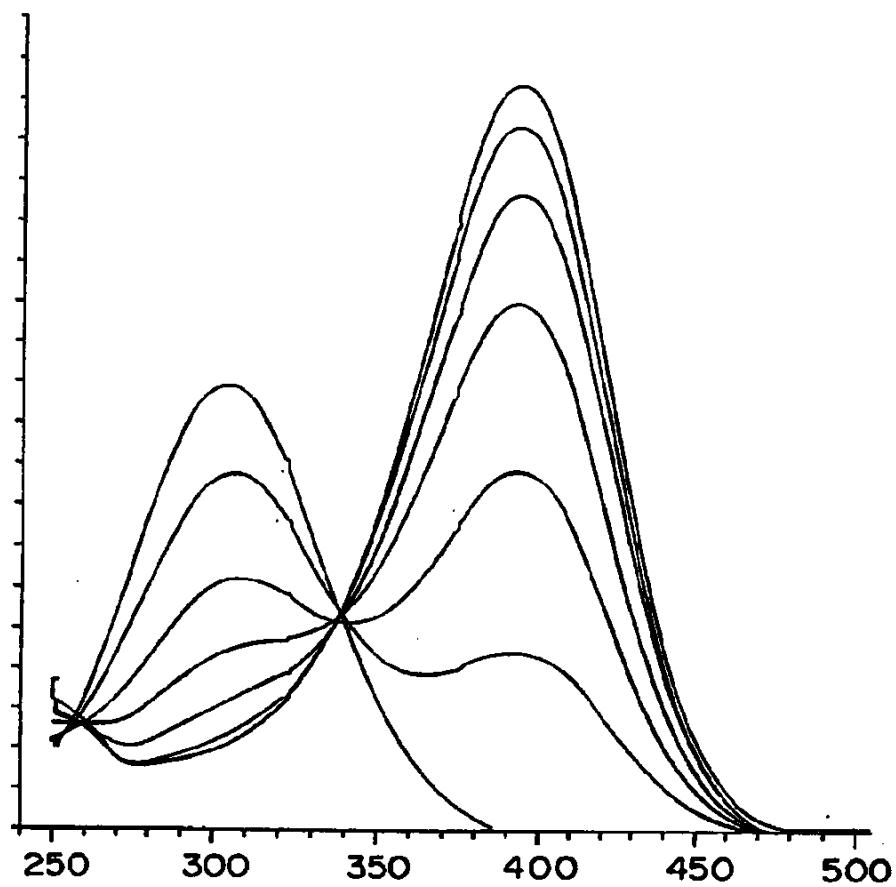


FIG. 13

Y % E

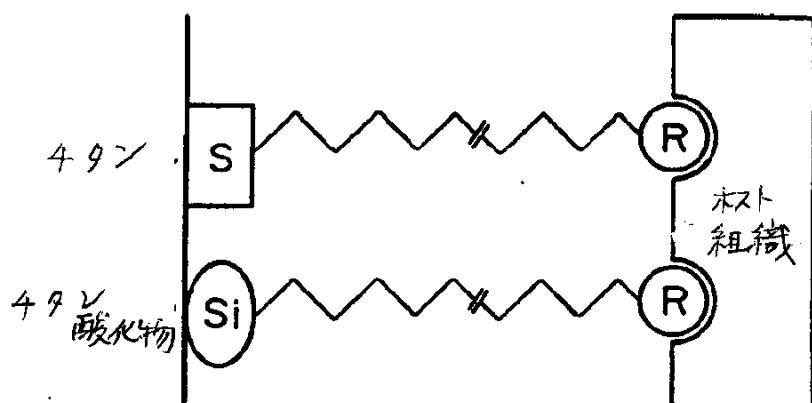
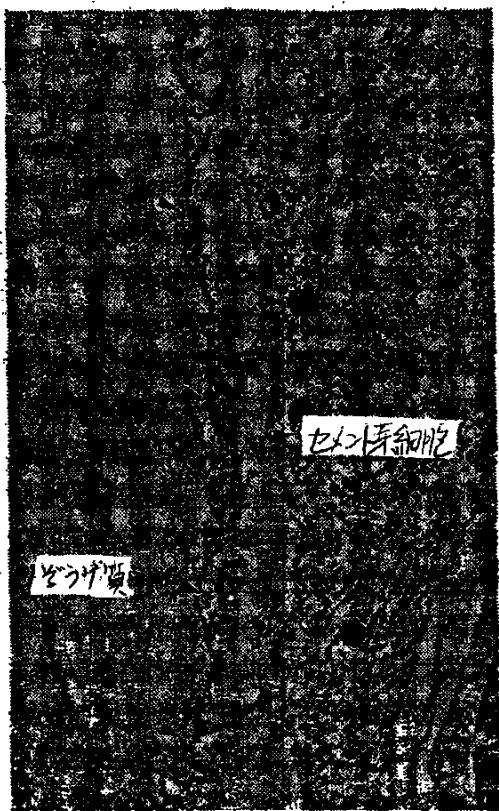


FIG. 15

Y } E

14A14B

O W A . ^ p N ɔ A O R R

X t F [g A z X z Z A S z X t

A

X z A r z X z l [g A z X z l [

t F [g A J { L V A y a

y v ' h z æ ' I † ɔ ø ɔ

S D O L A - " ' ^ A X e X

o ^ / W j " ... a ^ I e † ɔ ø

L o C I A

T D o C I A N e B u / ø

i j fi A - ¥ °

i j H i j o L » A - ¥

A N e B u /

o

U D H i j " f - | u ^ m [

X ^ e B b N d C » w I / ø

V D H i j a A f - | u ^

V I X ^ e B b N d C » w I / ø

ø

W D O L | e V I X ^ e B b N d C

ø A A - " ' ^ » ɔ

X D o C I A N e B u / ø A

i j fi A - ¥ °

i j H i j » A - ¥

i j H i j o L E - f

i j H i j A - ¥ ° ɔ

O L A - ¥ ° / L ɔ † " »

o

P O D O L ~ — » " — o b t @ █
 W L B
 P P D 1 x ' fi A — ¥ ° »
 ° f — | u ^ m [| ^ m [█
 » w I / ' ~ E — f █
 P Q D O L | e V I X ^ e B b N d █
 ‡ E A A — " ' ^ ' » c █
 P R D E — f fi A — ¥ ° \$ ~ █
 B █

Y + 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 94/00257A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 109 061 (PFAUDLER-WERKE AG.) 23 May 1984 see claims	1
A	WO,A,90 00887 (BIO-METRIC SYSTEMS, INC.) 8 February 1990 see claims; examples	1

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 August 1994	26.08.94
Name and mailing address of the ISA European Patent Office, P.B. 3818 Patentlaan 2 NL - 2280 Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer ESPINOSA, M

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern'l Application No
PCT/CA 94/00257

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0109061	23-05-84	DE-A-	3241589	17-05-84
		AU-B-	567310	19-11-87
		AU-A-	2111183	17-05-84
		BE-A-	898186	01-03-84
		CA-A-	1229953	08-12-87
		DE-A-	3377264	11-08-88
		JP-A-	59103660	15-06-84
		US-A-	4652459	24-03-87
WO-A-9000887	08-02-90	EP-A-	0425485	08-05-91
		US-A-	5002582	26-03-91

